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EDITORIAL COMMENT

The Remnants of Residual Risk*

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Despite the success of statin therapy in reducing atherosclerotic cardiovascular disease (ASCVD), there remains a large residual risk for recurrent events in statin-treated patients (1). Although residual risk may be attributable to many factors (i.e., smoking, elevated glucose, or blood pressure), there is considerable interest in lipoprotein-related residual risk beyond low-density lipoprotein (LDL)-cholesterol reduction obtained with the use of statins. Triglycerides (TGs), a surrogate marker of TG-rich remnant lipoproteins (remnants), have been a particular source of interest because of a consistent association with ASCVD and the increase in TG levels associated with the obesity epidemic (2).

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In this issue of the *Journal*, Schwartz et al. (3) leveraged 2 complementary trials to examine the association of fasting TG levels with recurrent ASCVD in statin-treated participants. The investigators performed post-hoc analyses of 1,501 participants from the short-term MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial, performed in the late 1990s, and 15,871 participants from the recent longer-term dal-OUTCOMES (A Study of RO4607381 in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome) trial (4,5). These trials provide fascinating snapshots of the eras in which they were conducted and demonstrate the evolution of secondary prevention strategies. The authors found a consistent, significant, 50% to 60% increase in hazard for recurrent events among those in the highest TG categories compared with those in the lowest, after adjustment for several risk factors and independent of LDL-cholesterol levels (3).

The differences between the trials merit attention. The event rate among statin-treated patients (i.e., residual risk) was strikingly high at 15% over only 16 weeks in MIRACL. This was markedly improved a decade later, though still high at nearly 8% over 31 months in dal-OUTCOMES. Both trials enrolled patients shortly after ACS, although MIRACL participants did not undergo revascularization, which had become standard of care by the time dal-OUTCOMES was conducted. The difference in treatment strategies probably contributed to the discrepancy in event rates while also providing a spectrum of risk ranging from the lower-risk dal-OUTCOMES population to the higher-risk, statin-naive MIRACL population. The consistent association of TG with risk across these diverse populations is timely, given recent findings related to ASCVD and remnants.

Just as LDL-cholesterol serves as a surrogate measure of LDL particles, TGs serve as a surrogate measure of remnant lipoproteins. Whereas LDL particles directly contribute to atherosclerosis, there has been uncertainty over the direct contribution of remnants to atherosclerosis because of their larger size. However, a series of Mendelian randomization studies have elegantly supported a causal role for remnants in atherosclerosis (6–9).

In a large Danish population, investigators found that genetic elevations in nonfasting TGs led to a nearly 90% increased odds of myocardial infarction (6). Similarly, Varbo et al. (7) showed a 2.8-fold higher causal odds of ischemic heart disease for each 39-mg/dl increase in remnant cholesterol (estimated

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as TG/5). Finally, 2 studies showed that a loss of function of apoC3, a key inhibitor of remnant metabolism, led to a lifetime of low remnant levels (as marked by TGs) and markedly reduced ASCVD (8,9).

The findings of Schwartz et al. (3) are consistent with a post-hoc analysis of short-term follow-up in the PROVE IT-TIMI 22 Trial, which also showed a reduction in recurrent events with lower on-treatment TG levels in statin-treated participants, independent of LDL-cholesterol (10). The present study extends these findings to more participants over longer follow-up periods. Future work can examine the risk associated with more direct measures of remnants, such as remnant lipoprotein cholesterol levels obtained by ultracentrifugation, rather than surrogates, such as TGs.

The questions of whether residual risk for recurrent ASCVD can be attributed to remnant lipoproteins, and to what degree, carry significant potential therapeutic implications. With the rise in metabolic syndrome and resultant increases in remnants, lifestyle modifications take on even greater importance as part of a structured preventive program. Inspired by the simple elegance of the iconic Jackson 5, we prefer the ABCs approach to prevention (11). Specifically, modest weight loss may reduce TG by ~20% and moderate to intense physical activity may reduce TGs by ~20% to 30% (2).

Although clinicians are armed with many non-statin lipid-lowering therapies, trials assessing their efficacy to reduce residual risk beyond statin therapy have mostly disappointed (5,12,13), with the recent exception of ezetimibe. However, there was a strong suggestion of benefit from niacin and fibrates in the subgroup with elevated TG and low HDL-cholesterol (12,14). Eicosapentaenoic acid (EPA) ("fish oil"), a strong TG reducer, has also had an inconsistent effect on ASCVD (15,16). Two large event-driven trials testing the addition of EPA to statins should provide definitive evidence for this class (17,18). Furthermore, development of pharmacotherapies targeting remnants by inhibition of apoC3 is well underway (19).

Schwartz et al. (3) add strong support that a residually high TG level on statin therapy is a biomarker of risk. Only more compelling randomized, controlled trial results showing a reduction in ASCVD among participants on statins and undergoing intensive lifestyle therapy, but with residual remnant elevation, will tell us if TG or remnants in particular must be a target of pharmacotherapy. For now, clinicians and patients must follow the familiar exhortation of football coach Bill Belichick: "Do your job!" refers to comprehensive risk factor modification with the use of proven pharmacologic therapy and lifestyle modification to lower future ASCVD risk.

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